REMARKS/ARGUMENTS

By this Amendment, claim 6 is canceled, and claims 1, 4, 7-10, 12-14, 23 and 29 are amended. Claims 1-5 and 7-55 are pending, with claims 28 and 30-55 withdrawn from consideration pursuant to a restriction requirement.

Claim 1 is amended for improved clarity. Claim 4 is amended so that claim 5, which depends from claim 4, is no longer redundant. Claims 8-10 and 12 are amended to improve antecedent basis. Claims 13-14 are amended to improve antecedent basis and to include the endpoints of the recited ranges within the literal scope of each claim. Claim 29 is amended to correct a typographical error.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Rejections under 35 U.S.C. § 112

Claims 1-27 and 29 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement in the specification (assuming that the third paragraph of page 3 identifies the rejected claims omitted from the introductory paragraph of the rejection in the last paragraph of page 2). This rejection is respectfully traversed.

Examiner Chunduru made an essentially identical rejection in parent U.S. Patent Application Serial No. 09/664,827, filed September 19, 2000, which is incorporated by reference into the present application in its entirety. The evidence and arguments presented by Applicants in that application are also applicable to this application. The arguments are reproduced below in

modified form, with the evidence attached as noted.

An invention is patentably enabled if one of ordinary skill in the art could make or use the invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. See, e.g., MPEP § 2164.01 *citing* United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

The first step in an enablement analysis is to construe the claims. MPEP § 2164. Claim 1 specifies a method of creating a nucleic acid multiplex structure in which each strand is related to all other strands of the multiplex by adherence to Watson-Crick base-pairing rules or homologous binding base-pairing rules. The meanings of Watson-Crick bonding and homologous bonding in the context of the invention are provided in the application at page 39, lines 11-18:

> As used herein, the term "Watson-Crick bonding" is intended to define specific association between opposing pairs of nucleic acid (and/or nucleic acid analogue) strands via matched, opposing bases. While the formation of a Watson-Crick quadruplex may sometimes be referred to as a hybridization event herein, that is merely for convenience and is not intended to limit the scope of the invention with respect to how the formation of a Watson-Crick quadruplex can be best characterized.

and page 12, lines 8-13:

> The term "base-pairing rules" are those that define the specificity between one nucleic acid molecule and another nucleic acid molecule when the two bind to each other with specificity. Examples are Watson-Crick base pairing rules (G-C, and A-T or A-U) and homologous binding base-pairing rules (A-A, T-T, G-G, C-C, U-U).

Although the original disclosure does not explicitly disclose the interatom hydrogen bond

locations, distances and quantities like those of duplex DNA figure in the Office Action at page 5, such additional information is not necessary to "make or use" the claimed invention, which does not specify such nanoscale features of the invention. The working examples of the specification (which are improperly overlooked in the Office Action, which points to "the absence of any working examples" at page 8) show that Applicants were able to make and use the invention without undertaking detailed biophysical studies. See the attached Rule 132 Declaration of Dr. J. Hans van de Sande (hereinafter the "JHS Declaration") at, e.g., paragraph 7, which was originally submitted in the parent application. Likewise, one of ordinary skill in the art (whom the Office Action acknowledges has a high level of skill) would be able to practice with no more than routine experimentation the claimed method without ever knowing for certain the location, length and/or number of hydrogen bonds between adjacent bases in the multiplexes formed therein. See the JHS Declaration at, e.g., paragraph 10.

Furthermore, Professor van de Sande cites an article (attached to his Declaration as Exhibit B) published subsequent to the filing of this application, which disproves the theory in the Office Action at page 6, last sentence, that "Watson-crick hydrogen bonding surfaces are inaccessible for any other strands [i.e., strands other than the two hybridized strands of conventional duplexes] since two strands are already interacting with each other at the center of the double helix." Zhang et al., "Dimeric DNA Quadruplex Containing Major Groove Aligned A•T•A•T and G•C•G•C Tetrads Stabilized by Inter-subunit Watson-Crick A•T and G•C Pairs," 312 J. Mol. Biol. 1073-88 (Oct. 5, 2001), shows through NMR studies the formation of A-T-A-T tetrads similar to previously discovered G-C-G-C tetrads. Zhang et al. at pages 1073-74 states:

[E]fforts have been made to identify and characterize G•C•G•C

> tetrads, where a pair of Watson-Crick G•C pairs can potentially align either through their major groove or their minor groove edges. . . . recent studies have demonstrated that G•C•G•C tetrads aligned through their major groove edges can switch between two distinct alignment geometries [shown in Figure 1(a) and 1(b)]. . . . The major groove-aligned G•C•G•C tetrad has now been observed in a range of DNA quadruplexes and appears to be a robust tetrad motif adopted by a wide range of DNA sequences.

Figure 1 of Zhang et al. shows how major groove-aligned G•C•G•C and A•T•A•T tetrads in their direct alignment geometry have each G hydrogen bonded to each C, and each A hydrogen bonded to each T. Thus, contrary to the Office Action, Zhang et al. and the art cited therein (whether prior or not) shows that Watson-Crick bonding pairs in a duplex are accessible for bonding to additional strands.

In summary, it should be apparent that the claimed invention is patentably enabled when the Wands Factors are properly applied. Contrary to the Office Action at page 9, line 7, the high skill level in the art is not the only factor favoring Applicants. Firstly, along with a high level of skill comes a high tolerance of experimental complexity. Secondly, the art does recognize the existence of triplex and quadruplex bonding. Thirdly, working examples **are** present in the original disclosure, despite the assertion to the contrary in the Office Action. The fact that the Office might prefer working NMR or crystallographic examples is no basis for completely ignoring the evidentiary weight of the extensive binding studies in the application, particularly in view of the JHS Declaration's explanation of the significance of the binding studies. Moreover, the working examples provided are much more relevant to practicing the claimed method than the requested biophysical studies.

In the parent application, the rejection was withdrawn in response to a February 3, 2003

Request for Reconsideration, which cited references showing space-filling model evidence supporting W-C base pairing involving more than two strands. Accordingly, the attached Information Disclosure Statement (IDS) cites the following references cited in the parent application:

(1) McGavin, "Models of Specifically Paired Like (Homologous) Nucleic Acid Structures," J. Mol. Biol. (1971) 55, 293-298 (hereinafter "McGavin 1");

(2) McGavin, "Relationships and Transformations Between Some Nucleic Acid Models," J. Theor. Biol. (1980) 85, 665-672 (hereinafter "McGavin 2");

(3) McGavin, "Four Strand Recombination Models," J. Theor. Biol. (1989) 136, 135-150 (hereinafter "McGavin 3");

(4) McGavin, "Four-Strand Structure, Kinks and Cruciforms in DNA," J. Theor. Biol. (1989) 138, 117-128 (hereinafter "McGavin 4"); and

(5) McGavin et al., "A Computer Graphics Study of Multistranded DNA Models," J. Mol Graphics. (1989) 7, 218-232 (hereinafter "McGavin 5").

The references track the development of theoretical multiplex nucleic acid models by Stewart McGavin of the University of Dundee (Scotland) over almost twenty years of research.

McGavin 1 discloses a theoretical model for quadruplex nucleic acid sequences based on the Watson-Crick base tetrads depicted on pages 293-95. McGavin 1 proposes models for the assembly of these previously postulated tetrads into nucleic acid sequences, wherein the tetrads are "stacked on top of each other." McGavin 1 at 293. According to McGavin 1 at the fifth full

paragraph on page 296:

> Preliminary work with models (Courtauld space filling) shows that there is no difficulty in building four-stranded structures in which two helices of the Watson-Crick-Wilkins type are related by a dyad axis parallel to the long molecular axis (Plate I).

Plate I of McGavin 1 is a photograph of the resulting "space filling model."

McGavin 2 further elaborates on the earlier publication, and at page 668 mentions the possibility of three-stranded structures based on the same kind of Watson-Crick "bonding system." Although McGavin 2 refers back to Plate I of McGavin 1 for a photograph of the four-strand model, Fig. 1 of McGavin 2 is a photograph of the "core structure" of the space-filling model.

McGavin 3 "develop[s] the idea that synapsis of DNA duplexes might take place by Watson-Crick base pairing between essentially intact duplex structures to form the .... same regular and compact four strand structure already discussed" in McGavin 1 and 2. See the Abstract of McGavin 3. Figs. 1 and 2 of McGavin 3 contain additional depictions of four-stranded nucleic acids based on Watson-Crick base interaction.

McGavin 4 discloses computer graphic models of four-stranded nucleic acids based on Watson-Crick base interaction. In the Introduction, the models are specifically distinguished from the "homopolynucleotide" structures disclosed by, e.g., Sen et al., Nature, 334, 364-66 (1988), which Applicants have previously distinguished from their invention.

McGavin 5 contains more detailed computer graphic models of four-stranded nucleic acids based on Watson-Crick base interaction, including the "basic four-strand structure" first

described in McGavin 1. Color Plate 2(a) shows the computer-generated model corresponding to the original space-filling model of McGavin 1. The computer modeling of McGavin 5 adds quantitative support to the earlier postulated space-filling models. For example, McGavin 5 reports at page 231:

The total energy of the four-strand model itself is slightly lower than twice that of either of its duplex components taken separately (that is, than two components of the Watson-Crick kind of two components of the "alternative" kind (2c)). The four-strand structure involves more interactions of the van der Waals kind, and also of the electrostatic kind, than the sum of two components of either kind taken separately.

Such quantitative calculations suggesting the thermodynamic favorability of four-stranded Watson-Crick complexes lend further credence to the existence of such complexes and the invention claimed by Applicants.

In view of the fact that Applicants have provided several independently authored references from several different scholarly journals showing quadruplex and triplex models based on Watson-Crick base interaction, as well as Declaratory evidence in support of the enablement of the invention, reconsideration and withdrawal of the rejection of claims 1-27 and 29 as being non-enabled are respectfully requested.

Claims 7 and 23 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. This rejection is obviated by the amendments to claims 7 and 23, which substitute alternative language for the expression "and/or". Accordingly, reconsideration and withdrawal of the rejection of claims 7 and 23 as being indefinite are respectfully requested.

Double Patenting Rejection

The obviousness-type double patenting rejection of claims 1-27 and 29 as being unpatentable over claims 1, 8-9, 17-18, 20, 24, 26-27, 29-30 and 32-37 of U.S. Patent No. 6,420,115 is obviated by the attached Terminal Disclaimer. Accordingly, reconsideration and withdrawal of the double patenting rejection of claims 1-27 and 29 are respectfully requested.

Rejection under 35 U.S.C. § 102

Claims 1-2 and 18-22 stand rejected under 35 U.S.C. § 102(e), as allegedly being anticipated by U.S. Patent No. 6,461,810 to Fresco et al. This rejection is respectfully traversed.

Fresco et al. does not disclose triplexes formed from heteropolymeric sequences. Fresco et al. discloses triplexes in which a polypurine (or polypyrimidine) region of a first strand is bonded in a Watson-Crick manner to a polypyrimidine (or polypurine) region of a second strand, and a third strand is bonded to the first strand by Hoogsteen hydrogen bonds. See Fresco et al. at column 2, lines 8-12, column 5, lines 12-16, the examples and Fig. 1B. As shown in Fig. 1B of Fresco et al., bonding occurs only in the homopolymeric portions of the triplex. The boxed portion of the duplex is not homopolymeric, but does not bond to the third strand.

Moreover, claim 1 requires all strands to adhere to base Watson-Crick or homologous base pairing rules. Fresco et al. teaches that the third strand bonds to the first strand by Hoogsteen base pairing rules.

Although the foregoing differences are sufficient to overcome the rejection, Applicants amend claim 1 to incorporate the limitations of claim 6 to provide a quantitative definition of

"heteropolymeric" by reference to the percentage of purine-pyrimidine and/or pyrimidine-purine dimers occurring throughout the duplex component of the complex. Thus, referring to Fig. 1B of Fresco et al., the percentage of such dimers is (3/19 or 16%), which is much less than the amount specified in claim 1 (i.e., more than 25%).

Accordingly, reconsideration and withdrawal of the rejection of claims 1-2 and 18-22 as being anticipated by Fresco et al. are respectfully requested.

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
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July 21, 2003

By _____

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.